

# Heart Rate Adjustment of Exercise-Induced ST Segment Depression

## Improved Risk Stratification in the Framingham Offspring Study

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**Background.** Simple heart rate adjustment of ST segment depression during exercise ( $\Delta$ ST/HR index) and the pattern of ST depression as a function of heart rate during exercise and recovery (the rate-recovery loop) have been shown to improve the ability of the exercise electrocardiogram to detect the presence of coronary heart disease (CHD), but the performance of these methods for the prediction of future coronary events remains to be examined.

**Methods and Results.** We compared the  $\Delta$ ST/HR index and the rate-recovery loop with standard electrocardiographic criteria for prediction of CHD events in 3,168 asymptomatic men and women in the Framingham Offspring Study who underwent treadmill exercise electrocardiography and who, at entry, were free of clinical and electrocardiographic evidence of CHD. After a mean follow-up of 4.3 years, there were 65 new CHD events: four sudden deaths, 24 new myocardial infarctions, and 37 incident cases of angina pectoris. When a Cox proportional hazards model with adjustment for age and sex was used, a positive exercise electrocardiogram by standard criteria ( $\geq 0.1$  mV horizontal or downsloping ST segment depression) was not predictive of new CHD events ( $\chi^2=0.40$ ,  $p=0.52$ ). In contrast, stratification according to the presence or absence of a positive  $\Delta$ ST/HR index ( $\geq 1.6$   $\mu$ V/beat/min) and a positive (counterclockwise) rate-recovery loop was associated with CHD event risk ( $\chi^2=9.45$ ,  $p<0.01$ ) and separated subjects into three groups with varying risks of coronary events: high risk, when both tests were positive (relative risk 3.6; 95% confidence interval, 2.4–5.4); intermediate risk, when either the  $\Delta$ ST/HR index or the rate-recovery loop was positive (relative risk, 1.9; 95% confidence interval, 1.3–2.8); and low risk, when both tests were negative. After multivariate adjustment for age, sex, smoking, total cholesterol level, fasting glucose level, diastolic blood pressure, and electrocardiographic evidence of left ventricular hypertrophy, the combined  $\Delta$ ST/HR index and rate-recovery loop criteria remained predictive of coronary events ( $\chi^2=5.45$ ,  $p=0.02$ ).

**Conclusions.** Heart rate adjustment of ST segment depression by the  $\Delta$ ST/HR index and the rate-recovery loop during exercise electrocardiography can improve prediction of future coronary events in asymptomatic men and women. (*Circulation* 1991;83:866–874)

Heart rate-adjusted indexes of ST segment depression during exercise and recovery that have high specificity in clinically normal subjects have improved the ability of the electrocardiographic exercise test to detect and assess the severity of coronary heart disease (CHD) in populations undergoing angiography.<sup>1–14</sup> However, test performance is highly dependent on population prevalence and severity of CHD<sup>15–18</sup> and on multiple

sources of bias in selecting patients for inclusion in clinical studies.<sup>19,20</sup> As a result, the value of the electrocardiographic exercise test as a screening technique for identifying CHD in low-risk populations remains controversial.<sup>21–24</sup>

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Recent work demonstrated that heart rate adjustment of ST segment depression during exercise can reduce the number of false-positive test responses in asymptomatic men while preserving test sensitivity for detecting occult CHD.<sup>25</sup> Despite these cross-sectional correlations, the value of these methods for predicting future coronary events in otherwise clinically normal subjects remains to be examined. Therefore, the purpose of this study was to compare

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performance of the  $\Delta$ ST segment/heart rate (ST/HR) index<sup>3,12,13,25</sup> and the rate–recovery loop<sup>14</sup> with standard electrocardiographic exercise test criteria for predicting future CHD events in relatively unselected, asymptomatic men and women without clinically evident CHD.

## Methods

### Study Population

Between 1971 and 1975, offspring of the original Framingham Heart Study cohort and spouses of the offspring were enrolled in a prospective study of cardiovascular diseases.<sup>26</sup> All subjects underwent a complete history and physical examination, resting electrocardiography, and determination of serum cholesterol and blood glucose levels. From 1979 to 1982, members of the cohort returned for a second examination and a treadmill exercise test. Of the 3,865 subjects who returned for a second examination, 347 subjects (9%) did not perform exercise and were not included in this analysis: 168 subjects had medical contraindications to exercise; 70 subjects were unable to walk on the treadmill; 37 subjects had a new diagnosis of myocardial infarction, angina, congestive heart failure, valvular heart disease, or syncope since the first examination; 15 subjects refused to participate; seven subjects were older than 70 years; and 50 subjects were rescheduled to a later date and never returned. Thus, the present study population was drawn from the 3,518 subjects who underwent exercise testing at the time of the second examination.

Of the 3,518 subjects who underwent exercise testing, 350 (10%) were excluded from further analysis: 67 subjects because of known or suspected CHD (Q wave myocardial infarction on the resting electrocardiogram); 41 subjects with a conduction abnormality on their resting electrocardiogram and 22 subjects taking digoxin because of possible interference with interpretation of the ST segment response to exercise; five subjects in atrial fibrillation; and 215 subjects in whom inadequate data were available to allow for either standard or heart rate–adjusted criteria of ST segment depression to be calculated. Thus, included in the present study were 3,168 asymptomatic subjects under 70 years of age and free of evidence of prevalent CHD, who underwent electrocardiographic treadmill exercise testing and subsequent 4-year follow-up. There were 1,521 men and 1,647 women whose mean age was  $44 \pm 10$  years (range, 17–70 years).

### Electrocardiographic Exercise Testing

Electrocardiographic exercise testing was performed on a treadmill according to the standard Bruce protocol.<sup>27</sup> Age- and sex-adjusted target heart rates, based on 85% of predicted maximal response, were sought as the exercise end point for all studies, but exercise was terminated when necessary because of the development of limiting fatigue, significant

angina or dyspnea, ST segment depression greater than 2 mm, significant ventricular ectopy, or a decrease in systolic blood pressure. ST segment depression was measured by computer to the nearest 10  $\mu$ V at a point approximately 80 msec after the J-point before exercise, after each stage of exercise, at peak exercise, immediately in the recovery period, and every minute for the first 4 minutes of recovery.

Exercise tests were evaluated by standard electrocardiographic criteria measured from the peak exercise tracings in each study.<sup>13,28</sup> The test was considered positive in the presence of 0.1 mV of additional horizontal or downsloping ST segment depression at the end of exercise, corrected for any resting ST depression in that lead on the upright preexercise control electrocardiogram.

### Heart Rate–Adjusted ST Segment Depression Criteria

Calculation of the  $\Delta$ ST/HR index and construction of the rate–recovery loop in all subjects were performed by investigators at the New York Hospital–Cornell Medical Center, who were unaware of age and sex of subjects and of all outcome data. The  $\Delta$ ST/HR index was calculated by dividing the maximal, additional ST segment depression at end exercise, corrected for any resting ST segment depression in that lead on the upright preexercise control electrocardiogram, by the exercise-induced change in heart rate.<sup>12,13,25,29</sup> A positive  $\Delta$ ST/HR index was defined as a value of 1.6  $\mu$ V/beat/min or more, based on previous studies.<sup>13,25</sup> Calculation of the maximal ST/HR slope was not performed in this study because of the large heart rate increments between stages of the Bruce protocol,<sup>27,30,31</sup> which has been shown to adversely affect ST/HR slope accuracy and to result in a large proportion of incalculable ST/HR slopes.<sup>7,11,30,31</sup>

The recovery phase pattern of ST segment depression with reference to changing heart rate (the rate–recovery loop) was examined by constructing continuous plots of absolute ST segment deviation and heart rate throughout treadmill exercise and recovery.<sup>14</sup> For each subject, ST segment depression was plotted in the upward direction on the vertical axis, as a function of heart rate during exercise and recovery on the horizontal axis; the resulting loop pattern was determined by the relation of early recovery phase ST depression to end-exercise ST depression at corresponding heart rates.

In clinically normal subjects, because less ST segment depression is present at early recovery phase heart rates than at corresponding exercise heart rates, there is a clockwise loop of ST segment depression as a function of heart rate during exercise and recovery. This pattern was defined as a normal rate recovery loop.<sup>14</sup> In patients with CHD, because ST segment depression is usually greater at early recovery phase heart rates than at corresponding exercise phase heart rates, there is a counterclockwise loop of ST segment depression as a function of the heart rate during exercise and recovery.<sup>14</sup> This pattern was defined as an abnormal rate–recovery loop.

### Risk Factor Analysis

Risk factors were measured at the time of the exercise test and included age, sex, diastolic blood pressure, fasting blood glucose level, total serum cholesterol level, electrocardiographic left ventricular hypertrophy, and cigarette smoking. Age, diastolic blood pressure, blood glucose level, and total cholesterol level were recorded as continuous variables, whereas sex, left ventricular hypertrophy, and cigarette smoking were scored as dichotomous variables. The procedures and criteria for determining risk factors were previously outlined in detail.<sup>32</sup>

### Determination and Definition of Events

Four-year follow-up information and vital status were available on all 3,168 subjects included in this report. Criteria for each cardiovascular outcome during follow-up were standardized,<sup>32</sup> and decisions regarding diagnosis were made by a panel of Framingham investigators. CHD events included new onset of angina pectoris, evidenced by a typical history of chest pain according to a physician-administered questionnaire; coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on the electrocardiogram; myocardial infarction, determined by two of three clinical criteria (specified electrocardiographic changes, prolonged chest discomfort, and diagnostic elevation of serum enzymes) or by myocardial infarction at autopsy; and sudden (in less than 1 hour) or nonsudden coronary death.<sup>32</sup>

### Statistical Methods and Data Analysis

Cumulative event rates for positive and negative exercise test variables are initially reported as the raw event rates, with relative risk (RR) of a positive test and its 95% confidence interval (CI).<sup>33</sup> Event-free survival rates according to each method were plotted according to the method of Kaplan and Meier,<sup>34</sup> with comparisons of event-free survival performed with the log-rank test.<sup>35</sup> Simple age- and sex-adjusted Cox proportional hazards models<sup>36</sup> were then used to test the predictive value of each exercise test criterion for CHD events. Exercise test results for standard criteria, the  $\Delta$ ST/HR index, and the rate-recovery loop were coded as dichotomous variables (positive or negative as previously defined).

Based on the complementary information contained in the two heart rate-adjusted methods,<sup>14</sup> a combined test criterion was derived that incorpo-

TOTAL POPULATION (n=3168)

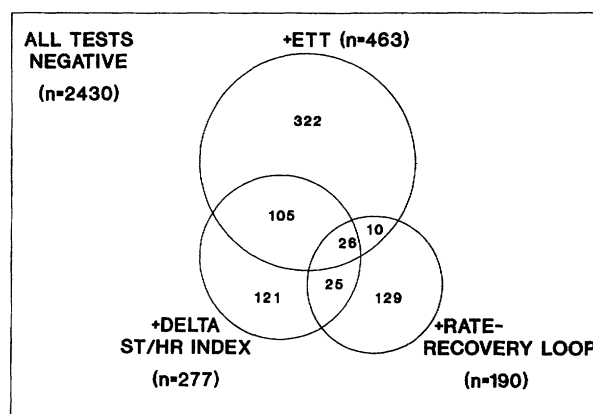


FIGURE 1. Venn diagram illustrating the overlap of positive  $\Delta$ ST segment/heart rate index and rate-recovery loop responses with positive and negative standard electrocardiographic responses. Numbers indicate number of subjects with the observed test responses. ETT, standard exercise electrocardiogram. HR, heart rate.

rated both the  $\Delta$ ST/HR index and the rate-recovery loop. Raw 4-year survival data were calculated with the combined test criterion coded as a four-way variable: both tests positive, the  $\Delta$ ST/HR index positive and rate-recovery loop negative, the rate-recovery loop positive and the  $\Delta$ ST/HR index negative, or both tests negative. Based on the similar risk stratification attributable to either a positive  $\Delta$ ST/HR index and negative rate-recovery loop finding or a positive rate-recovery loop and negative  $\Delta$ ST/HR index finding, a simplified three-tiered criterion was derived and examined with Kaplan-Meier plots and a simple age- and sex-adjusted Cox model.<sup>34-36</sup> Last, a multivariate Cox model was derived that included the combined  $\Delta$ ST/HR index and rate-recovery loop variable, age, sex, cigarette smoking, diastolic blood pressure, total cholesterol level, fasting glucose level, and electrocardiographic left ventricular hypertrophy.<sup>36</sup>

With the proportional hazards models, the estimated relative risk of the incidence of a CHD event for a positive test outcome, compared with a negative test outcome, was computed as the antilog of the estimated coefficient corresponding to the dichotomous variable.<sup>37</sup> When the electrocardiographic outcome was coded in a three-way category, risks relative to negative test outcomes were computed in the same manner.

TABLE 1. Cumulative Coronary Heart Disease Event Rates and Relative Risks According to Exercise Test Criteria

Criteria	Event rate				Relative risk	95% CI
	+Test		−Test			
	<i>n</i>	%	<i>n</i>	%		
ΔST/HR index	15/277	5.4	50/2,891	1.7	3.1	1.7–5.6
Rate–recovery loop	10/190	5.3	55/2,978	1.8	2.9	1.4–5.7
Standard ECG	13/463	2.8	52/2,705	1.9	1.5	0.8–2.7

CI, confidence interval;  $\Delta$ ST/HR index,  $\Delta$ ST segment/heart rate index; ECG, electrocardiogram.



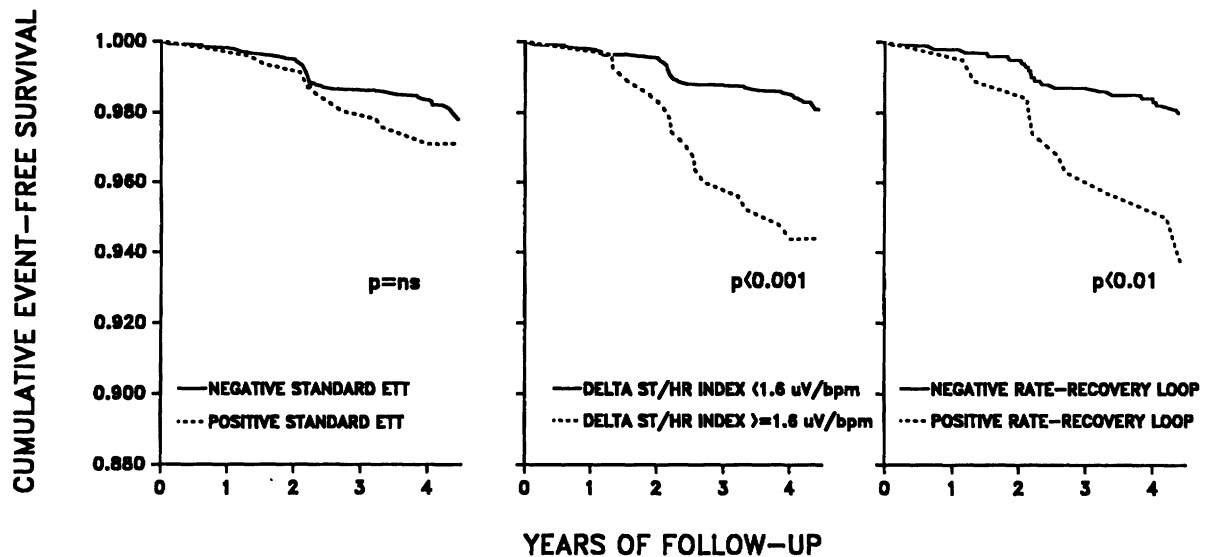


FIGURE 2. Kaplan-Meier plots of event-free survival according to exercise test criteria. ETT, standard exercise electrocardiogram; HR, heart rate.

95% CI for the increased risk associated with a positive test outcome were calculated from the estimated coefficient for a positive test and its standard error.<sup>38</sup>

### Results

Among the 3,168 subjects, after a mean follow-up of 4.3 years, there were 65 new CHD events (0.5%/yr incidence). There were four deaths due to sudden cardiac arrest, 24 cases of new myocardial infarctions, and 37 cases of new onset angina. The prevalence and overlap of test responses for each exercise criterion are shown in Figure 1. A high proportion of positive  $\Delta$ ST/HR index responses (53%, 146 of 277) and most positive rate-recovery loops (81%, 154 of 190) occurred in subjects with negative responses by standard electrocardiographic exercise test criteria.

#### Prediction of Coronary Events by Standard and Rate-Adjusted Criteria

Cumulative CHD event rates for subjects with positive and negative exercise tests according to each method are compared in Table 1. Cumulative risk of a new CHD event was significantly higher in subjects with a positive  $\Delta$ ST/HR index (5.4%) than in subjects with a negative  $\Delta$ ST/HR index (1.7%,  $p<0.001$ ), and the RR of an event in subjects with a positive test was more than three times that of subjects with a negative test. CHD event risk was similarly concentrated in subjects with a positive rate-recovery loop compared

with subjects with a normal rate-recovery loop (5.3% versus 1.8%; RR, 2.9;  $p<0.01$ ). In contrast, CHD event risk was only weakly concentrated among subjects with a positive test compared with subjects with a negative standard electrocardiographic exercise test (2.8% versus 1.9%; RR, 1.5;  $p=NS$ ).

Because the prognostic power of a method is highly dependent on the time to event, risk stratification according to these methods was further examined with Kaplan-Meier survival curves (Figure 2). When adjusted for time to occurrence of CHD events, both the  $\Delta$ ST/HR index and rate-recovery loop remained highly predictive of outcome, with significantly lower event-free survival rates among subjects with positive than those with negative test outcomes. In contrast, there was no significant difference in the event-free survival time between subjects with positive and those with negative standard exercise tests defined according to traditional electrocardiographic criteria.

When baseline risk was further adjusted for age and sex (Table 2), both a positive  $\Delta$ ST/HR index and an abnormal rate-recovery loop remained independent predictors of CHD events, with RR of 2.2 and 2.1, respectively. In contrast, a positive test according to standard electrocardiographic criteria was not associated with a significant increase in CHD events ( $\chi^2=0.40$ ,  $p=0.52$ ) when baseline risk was adjusted for both age and sex. Inclusion of upsloping ST

TABLE 2. Age- and Sex-Adjusted Proportional Hazards Model for Prediction of Coronary Heart Disease Event Risk According to Exercise Test Criteria

Criteria	$\chi^2$	$p$	Relative risk	95% CI
$\Delta$ ST/HR index	6.42	0.01	2.2	1.2–3.9
Rate-recovery loop	4.59	0.03	2.1	1.1–4.2
Standard ECG	0.40	0.52	1.2	0.7–2.2

CI, confidence interval;  $\Delta$ ST/HR index,  $\Delta$ ST segment/heart rate index; ECG, electrocardiogram.

**TABLE 3. Cumulative Coronary Heart Disease Event Rates and Relative Risk According to Combined  $\Delta$ ST/HR Index and Rate-Recovery Loop Criteria**

Criteria*	Event rate		Relative risk	95% CI
	n	%		
+ $\Delta$ /+loop	5/51	9.8	6.0	2.3–15.7
+ $\Delta$ /–loop	10/226	4.4	2.7	1.4–5.5
– $\Delta$ /+loop	5/139	3.6	2.2	0.9–5.6
– $\Delta$ /–loop	45/2,752	1.6	1.0	–

CI, confidence interval;  $\Delta$ ,  $\Delta$ ST segment/heart rate index; loop, rate-recovery loop.

\*Overall  $\chi^2=25.61$ ,  $p<0.001$ .

segment depression 0.1 mV or more in the definition of a positive standard electrocardiographic test response did not significantly improve risk stratification by standard criteria when baseline risk was adjusted for age and sex (RR, 1.4; 95% CI, 0.9–2.0).

#### Combined Rate-Adjusted Criteria

Because the rate-recovery loop provides diagnostic information distinct from heart rate adjustment of ST segment depression during exercise alone,<sup>14</sup> and based on the similar risk concentration found for a positive  $\Delta$ ST/HR index and a counterclockwise rate-recovery loop in the present study, we assessed the ability of combinations of these variables to predict CHD events. Four-year event rates for the combined  $\Delta$ ST/HR index and rate-recovery loop criteria are shown in Table 3. When both tests were positive, a small subset of subjects was identified who had a markedly increased risk of a CHD event during 4 years (9.8%, five of 51). In contrast, both tests were negative in a large subgroup with a significantly lower risk of developing CHD events (1.6%, 45 of 2,752). In the presence of a positive  $\Delta$ ST/HR index and normal rate-recovery loop, the risk of having a CHD event was intermediate (4.4%, 10 of 226) and was similar to the risk when the rate-recovery loop was abnormal and the  $\Delta$ ST/HR index was negative (3.6%, five of 139). When the results for these two “intermediate risk” groups were combined, the risk of having a CHD event was 4.1% (15 of 365) when either the  $\Delta$ ST/HR index or the rate-recovery loop was positive, with an RR of 2.5 as compared with when both tests were negative. The resulting three-tiered criteria based on the two heart rate-adjusted methods were then further examined in the context of their independence from other CHD risk factors.

When adjusted for time to coronary event, the combined criteria separated subjects into three groups with a high, intermediate, or low event-free survival for the 4-year period of follow-up (Figure 3). When baseline risk was further adjusted for age and sex (Table 4), the combined criteria remained highly predictive of CHD events, with an RR of 3.6 when both tests were positive and an RR of 1.9 when either the  $\Delta$ ST/HR index or the rate-recovery loop was positive. When baseline risk was further adjusted to account for diastolic blood pressure, cigarette smoking, total cholesterol level, fasting glucose level, and

the presence of left ventricular hypertrophy on the resting electrocardiogram, the combined criteria remained an independent predictor of CHD events (Table 4).

When analyzed for the separate prediction of myocardial infarction, new onset of angina, or death due to sudden cardiac arrest, the combined criteria also identified groups with low, intermediate, or high risk of single subsequent events. Cumulative risks of myocardial infarction, or of subsequent angina, were significantly higher when either the  $\Delta$ ST/HR index or the rate-recovery loop was positive (RR, 2.8; 95% CI, 1.1–7.2; and RR, 2.2; 95% CI, 1.0–4.9, respectively) and when both tests were positive (RR, 6.7; 95% CI, 1.5–30.1; and RR, 4.0; 95% CI, 1.0–17.3) than when both tests were negative. Similar trends were seen for risk of death due to sudden cardiac arrest, but the small number of these events during 4 years of follow-up precludes meaningful, separate, statistical analysis.

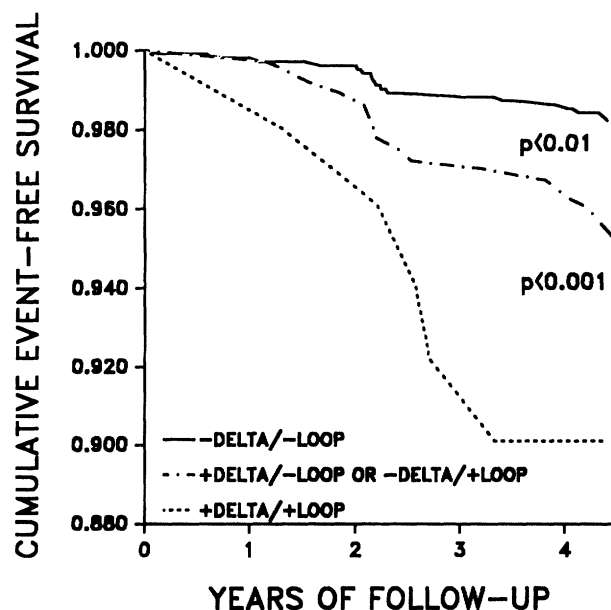


FIGURE 3. Kaplan-Meier plots of event-free survival according to combined  $\Delta$ ST segment/heart rate index and rate-recovery loop criteria. Delta,  $\Delta$ ST segment/heart rate index; Loop, rate-recovery loop.

**TABLE 4. Proportional Hazards Models for Combined  $\Delta$ ST Segment/Heart Rate Index and Rate-Recovery Loop Criteria**

	Relative risk	95% CI
Age- and sex-adjusted ( $\chi^2=9.45$ , $p=0.002$ )		
+ $\Delta$ /+loop	3.6	2.4–5.4
+ $\Delta$ /–loop or – $\Delta$ /+loop	1.9	1.3–2.8
– $\Delta$ /–loop	1.0	–
Multivariate* ( $\chi^2=5.31$ , $p=0.021$ )		
+ $\Delta$ /+loop	2.7	1.8–4.0
+ $\Delta$ /–loop or – $\Delta$ /+loop	1.6	1.1–2.5
– $\Delta$ /–loop	1.0	–

CI, confidence interval;  $\Delta$ ,  $\Delta$ ST segment/heart rate index; loop, rate-recovery loop.

\*Age, sex, cigarette smoking, diastolic blood pressure, total cholesterol level, fasting glucose level, electrocardiographic left ventricular hypertrophy.

The predictive values of the combined  $\Delta$ ST/HR index and rate-recovery loop criteria among subjects with negative and positive standard electrocardiographic exercise test responses are examined in Table 5. Among the large subset of subjects with negative standard electrocardiographic exercise tests, cumulative risk of CHD events remained higher when either the  $\Delta$ ST/HR index or rate-recovery loop was positive (RR, 1.9; 95% CI, 0.9–4.1) and when both tests were positive (RR, 7.1; 95% CI, 2.1–24.5) than when both tests were negative. Cumulative risk of CHD events was also significantly higher in subjects with positive standard electrocardiographic test responses when either the  $\Delta$ ST/HR index or rate-recovery loop was positive (RR, 4.9; 95% CI, 1.4–17.1) and when both tests were positive (RR, 6.2; 95% CI, 1.1–35.4) than when both tests were negative. Of note, when both the  $\Delta$ ST/HR index and rate-recovery loop were negative, risk of CHD events was no different in subjects with positive than in those with negative standard electrocardiographic test responses (1.2%, four of 322 versus 1.7%, 41 of 2,430,  $p=NS$ ).

The predictive values of the combined  $\Delta$ ST/HR index and rate-recovery loop criteria in men and women separately are examined in Table 6. Although the cumulative CHD event rate was significantly higher in men than in women (47 of 1,521, 3.1% versus 18 of 1,647, 1.1%;  $\chi^2=14.7$ ,  $p<0.001$ ), the combined criteria significantly stratified risk in each sex.

## Discussion

These data demonstrate that the two heart rate-adjusted indexes of ST segment depression each perform better than standard electrocardiographic exercise test criteria for stratifying the risk of future CHD events in asymptomatic subjects. In addition to superior test accuracy for identifying CHD,<sup>1–6,8,10,11,13,14,25</sup> heart rate adjustment of ST depression with the  $\Delta$ ST/HR index and the rate-recovery loop can provide useful prognostic information that is independent of established risk factors in otherwise clinically normal subjects. In contrast to previous studies of exercise electrocardiographic stratification of risk that have either excluded women<sup>39–43</sup> or included only small groups of women,<sup>44,45</sup> the present findings demonstrate that concentration of risk by heart rate-adjusted methods is significant in both women and men.

### Exercise Electrocardiographic Identification of Risk

Standard electrocardiographic exercise test criteria have been shown to stratify risk for further CHD events,<sup>39–45</sup> but our findings highlight the inherent limitations of screening for future coronary events in populations with a low prevalence of anatomic coronary obstruction.<sup>24,46,47</sup> Beyond the well-documented Bayesian principles that underlie the relatively poor sensitivity and positive predictive value of exercise testing for future events found in asymptomatic sub-

**TABLE 5. Cumulative Coronary Heart Disease Event Rates and Relative Risk by Standard Electrocardiographic Response According to Combined  $\Delta$ ST Segment/Heart Rate Index and Rate-Recovery Loop Criteria**

Criteria	Event rate		Relative risk	95% CI
	<i>n</i>	%		
– Standard ECG ( <i>n</i> =2,705)				
+Δ/+loop	3/25	12.0	7.1	2.1–24.5
+Δ/–loop or –Δ/+loop	8/250	3.2	1.9	0.9–4.1
–Δ/–loop	41/2,430	1.7	1.0	–
+ Standard ECG ( <i>n</i> =463)				
+Δ/+loop	2/26	7.7	6.2	1.1–35.4
+Δ/–loop or –Δ/+loop	7/115	6.1	4.9	1.4–17.1
–Δ/–loop	4/322	1.2	1.0	–

CI, confidence interval; ECG, electrocardiogram;  $\Delta$ ,  $\Delta$ ST segment/heart rate index; loop, rate-recovery loop.

**TABLE 6. Cumulative Coronary Heart Disease Event Rates and Relative Risk by Sex According to Combined  $\Delta$ ST Segment/Heart Rate Index and Rate-Recovery Loop Criteria**

Criteria	Event rate		Relative risk	95% CI
	<i>n</i>	%		
Men ( <i>n</i> =1,521)*				
+Δ/+loop	4/26	15.4	6.2	2.1–18.8
+Δ/−loop or −Δ/+loop	10/163	6.1	2.5	1.2–5.2
−Δ/−loop	33/1,332	2.5	1.0	—
Women ( <i>n</i> =1,647)†				
+Δ/+loop	1/25	4.0	4.7	0.6–37.6
+Δ/−loop or −Δ/+loop	5/202	2.5	2.9	1.0–8.3
−Δ/−loop	12/1,420	0.8	1.0	—

CI, confidence interval;  $\Delta$ ,  $\Delta$ ST segment/heart rate index; loop, rate-recovery loop.\*Overall  $\chi^2=19.8$ ,  $p<0.001$ ; †overall  $\chi^2=6.3$ ,  $p<0.05$ .

jects and patients,<sup>15–18</sup> the inability of exercise testing to identify the presence of non-flow-limiting coronary obstructions<sup>46,47</sup> and to predict the progression or new development of coronary lesions<sup>46,47</sup> are additional important factors. Although the presence of a mild, non-flow-limiting coronary obstruction would not be expected to produce an ischemic response to exercise,<sup>46</sup> catastrophic disruption of these lesions or superimposed thrombosis may result in subsequent myocardial infarction or death due to sudden cardiac arrest in some patients.<sup>46,47</sup> Moreover, sequential exercise testing in asymptomatic subjects has demonstrated that approximately 2% of subjects may convert to a positive exercise test each year.<sup>48,49</sup> These factors suggest reasons for the low sensitivity of baseline screening methods for identifying future risk in populations with a low prevalence of CHD at the time of initial evaluation.

Although these heart rate-adjusted methods can identify a small group of asymptomatic subjects at increased risk of CHD events with relatively high predictive value, the low overall sensitivity for future events argues against their routine use as a reliable, cost-effective screening method in such low-risk populations. These findings should be extrapolated with caution to other populations, but the improved accuracy of heart rate-adjusted methods for the presence and severity of coronary obstruction in patients with angina<sup>1–14,25</sup> and the improved accuracy of other methods that normalize ST depression for myocardial work load<sup>22</sup> suggest that heart rate-adjusted methods may also improve the electrocardiographic exercise test identification of future risk in more highly selected and symptomatic patients. Further study is necessary to evaluate the prognostic value of these methods in such higher risk populations.

In contrast to several previous studies,<sup>39–41,44,45</sup> standard electrocardiographic exercise test criteria did not significantly stratify risk in the present study. Differences in population selection, symptom status, and subject classification may explain these differences. An ischemic ST segment response to exercise was a significant predictor of morbidity and mortality due to cardiac causes in the overall population of the Seattle

Heart Watch<sup>44</sup> and in a referred group of clinically normal male Air Force personnel.<sup>40</sup> However, a positive standard ST segment response to exercise did not significantly concentrate risk among the large subset of asymptomatic, healthy subjects in Seattle<sup>44</sup> and, similarly, did not concentrate risk in an unreferred subgroup of normal pilots and astronauts undergoing exercise testing as part of a routine preflight evaluation.<sup>40</sup> These subgroups are more similar to our population. Differences in ST segment analysis,<sup>42,43,45</sup> as well as differences in exercise methodology,<sup>45</sup> may also play a role in the differing prognostic power found for ST segment depression in other studies.

#### *Heart Rate Adjustment of ST Segment Depression: Methodological Considerations*

The  $\Delta$ ST/HR index and the rate-recovery loop represent a more physiological approach to the interpretation of the ST segment response during exercise and recovery<sup>11–14,25,29</sup> and provide independent and complementary information regarding the presence and potential severity of underlying coronary obstruction.<sup>14</sup> The magnitude of ST segment depression during exercise can be directly related to the level of myocardial work load, as reflected by heart rate, in patients with myocardial ischemia. Because both the  $\Delta$ ST/HR index and ST/HR slope are continuous variables that reflect this relation in a quantitative fashion, their values can be accurately related to both the presence and severity of CHD.<sup>3,12,13,25,29</sup> In contrast, during early recovery, the magnitude of ST segment depression in patients with CHD generally remains greater than expected for the rapidly decreasing myocardial oxygen demand that results from an abrupt lowering of exercise load, producing a counterclockwise rate-recovery loop pattern.<sup>14</sup> Because direction of the rate-recovery loop is not dependent on a particular threshold magnitude of ST segment depression at peak exercise, sensitivity of this method for identifying CHD may be less affected by the anatomic and functional severity of underlying coronary obstruction than are standard and heart rate-adjusted criteria that are derived from exercise-phase data alone.<sup>14</sup>



Although the  $\Delta$ ST/HR index significantly concentrates risk in the present study, the more complex ST/HR slope method might have performed with greater accuracy. Although the ST/HR slope relates changing ST depression to heart rate changes occurring during maximum ischemia, the  $\Delta$ ST/HR index relates overall ST depression to the total heart rate change during exercise.<sup>12,13,25,29</sup> Because this total change in heart rate may include a variable period of effort during which ischemia is absent, the  $\Delta$ ST/HR index should not as effectively normalize ST depression for oxygen demand during ischemia as does the maximal ST/HR slope and, therefore, may not as accurately reflect the presence and severity of coronary obstruction.<sup>29</sup> Further study is necessary to evaluate the potential of this method to stratify risk of coronary events; this may be facilitated by the recent implementation of accurate, on-line computerized calculation of the ST/HR slope.<sup>50</sup>

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**KEY WORDS** • exercise electrocardiography • ST segment depression • heart rate • Framingham Offspring Study • risk stratification • coronary heart disease

## Heart rate adjustment of exercise-induced ST segment depression. Improved risk stratification in the Framingham Offspring Study.

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